Cyclosiloxanes Produce Fatal Liver and Lung Damage in Mice

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To examine the toxicity of cyclosiloxanes (CSs), the predominant low molecular weight cyclic silicones found in breast implants, we injected female CD-1 mice intraperitoneally with different doses of distillate (3.5–35 g/kg body weight) containing cyclosiloxane D3 (hexamethylcyclotrisiloxane; CS-D3), cyclosiloxane D4 (octamethylcyclotetrasiloxane; CS-D4), cyclosiloxane D5 (decamethylcyclopentasiloxane; CS-D5), and cyclosiloxane D6 (dodecamethylcyclohexasiloxane; CS-D6). The distillate was found to be lethal and all the mice injected with 35 g/kg died within 5–8 days. The median lethal dose (LD_{50}) for distillate was estimated to be approximately 28 g/kg. These mice developed inflammatory lesions of the lung and liver as well as liver cell necrosis with elevated serum levels of alanine aminotransferase, aspartate aminotransferase, and lactic acid dehydrogenase. Administration of CS-D4 alone also produced lethality in these mice with an LD_{50} of 6–7 g/kg. CS-D4-treated mice also exhibited pulmonary and hepatic lesions and elevated serum enzymes. Analysis of LD_{50} data indicates that CS-D4 is about as toxic as carbon tetrachloride or trichloroethylene. We measured hydroxyl radical formation in CS-D4-treated mice and found increases of approximately 20-fold in liver and approximately 7-fold in lung on day 4 following injection. Our findings are significant because *in vitro* experiments have demonstrated that CSs can migrate out of breast implants, and in mouse experiments CSs have been shown to be widely distributed in many organs after a single subcutaneous injection and to persist for at least a year. *Key words*: breast implants, cyclosiloxanes, silicone, toxicology. *Environ Health Perspect* 107:161–165 (1999). [Online 14 January 1999] *http://ehpnet1.niehs.nih.gov/docs/1999/107p161-165lieberman/abstract.html*

It has been estimated that at least 800,000 and perhaps as many as 2 million women have had silicone breast implants in the United States (*1–3*). In the past decade there has been widespread interest in the potential risk from exposure to the silicone present in these implants. In spite of the fact that many investigations have been undertaken, much remains to be learned about silicone biology. Implants are composed primarily of high molecular weight silicone polymers (polydimethylsiloxane) (*4*), but 1–2% of the contents of implants are low molecular weight silicones including cyclosiloxanes (CSs). These compounds are cyclic oligomers (n = 3–20) of dimethylsiloxane (e.g., Fig. 1A) and can migrate out of intact implants (*5–7*). In addition, it is known that implants may rupture and release their contents (*8,9*). We have recently shown that after a single subcutaneous injection of breast implant distillate [containing hexamethylcyclotrisiloxane (CS-D3), octamethylcyclotetrasiloxane (CS-D4), decamethylcyclopentasiloxane (CS-D5), and dodecamethylcyclohexasiloxane (CS-D6)], CSs were widely distributed throughout the body (*10*). These compounds were found in all of the 10 organs we examined and persisted for at least 1 year in them and in abdominal fat.

In addition to possible exposure from breast implants, other medical procedures may also expose patients to CSs. Low molecular weight siloxanes, including CSs, have been used in ophthalmology to treat retinal detachment (*11*). In spinal surgery, the use of soft silicone gels has the potential to expose patients to CSs (*12*). Also, in the past in cosmetic surgery, low molecular weight silicone oils containing CSs were used to remove wrinkles (*13*).

Such studies raise the question of whether CSs are toxic. Previously, most investigations have focused on high molecular weight silicone polymers (polydimethylsiloxane) (*14–16*); however, unless there is rupture of the implant, exposure to the polymer is unlikely. On the other hand, even without rupture, the transmigration of low molecular weight CSs from intact implants (*5–7*) indicates that many and perhaps all organs have the potential for exposure to these compounds (*10*). To examine the possible role of CSs in tissue injury, we undertook a series of experiments in which we administered breast implant distillate (containing CS-D3, CS-D4, CS-D5, and CS-D6) or CS-D4 alone to female mice. Our findings indicate that these compounds are highly toxic and produce extensive tissue injury and death in these mice.

Materials and Methods

Breast implants used in this study were explanted breast implants obtained after surgical removal from patients. Breast implant distillate was prepared from these implants as previously described (*5,17*). Gas chromatography/mass spectrometric (GC/MS) analysis revealed that the distillate consisted of a mixture of CS-D3 (18%), CS-D4 (60%), CS-D5 (20%), and CS-D6 (2%), with less than 1% low-molecular-weight linear siloxanes (Fig. 1B). The distillate also contained platinum (40 µg/kg distillate) as revealed by inductively coupled plasma mass spectroscopy (ICP/MS) (*5*). CS-D4 (Fig. 1A) was purchased from Ohio Valley Specialty Chemical (Marietta, OH) and was found to be more than 99% pure by GC/MS (and Pt-free); 2,3- and 2,5-dihydroxybenzoic acid (DHBA) were purchased from Sigma (St. Louis, MO). All the reagents and chemicals used were of analytical grade.

Exposure of mice to cyclosiloxanes. All animal use procedures were in strict accordance with the NIH *Guide for the Care and Use of Laboratory Animals* and were approved by the Baylor Animal Care Committee. For median lethal dose (LD_{50}) studies, groups (5–12 mice/group) of female CD-1 mice (8–10 weeks of age; 25–30 g body weight) were injected intraperitoneally with 1 ml soy oil (controls, ~32 g/kg), 0.1–1.0 ml (3.5–35 g/kg) breast implant distillate, or CS-D4. This dosage regimen was repeated with separate groups of mice for histological and biochemical studies. Soy oil-treated mice served as controls throughout these experiments. Food and water were provided *ad libitum*. For LD_{50} studies, mice were followed for 14 days. Mice that were clearly moribund were sacrificed. Results were tallied as number died per number injected. At 14 days, survivors were sacrificed by CO_2 narcosis followed by cervical dislocation. For histopathology and biochemical studies, separate groups of mice (4–6/group) were injected with distillate or CS-D4 and were sacrificed at 4 or 14 days. Blood samples collected from the rear orbital sinus of these mice were used to measure aspartate aminotransferase (AST), alanine aminotransferase (ALT), and lactic acid dehydrogenase (LDH) levels. For the hydroxyl radical measurement studies, separate groups of mice (4/group) were injected with 8.75 g/kg CS-D4 or soy oil and sacrificed at 1 or 4 days after treatment to determine the 2,3-DHBA formation in liver and lung tissues.

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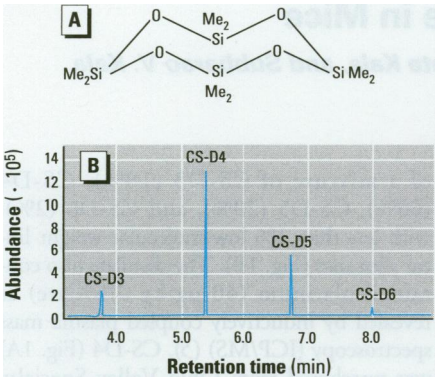

Figure 1. The structure of octamethylcyclotetrasiloxane (CS-D4) and proportions of cyclosiloxanes (CSs) in breast implant distillate. (A) Molecular structure of CS-D4. (B) Gas chromatography/mass spectrometric analysis of breast implant distillate (90 ng). Abbreviations: CS-D3, hexamethylcyclotrisiloxane; CS-D5, decamethylcyclopentasiloxane; CS-D6, dodecamethylcyclohexasiloxane. We used Wiley library mass spectral data to confirm the presence of individual CSs. The relative proportion of each compound was approximately 18, 60, 20, and 2% for CS-D3, CS-D4, CS-D5, and CS-D6, respectively.

Table 1. Mortality after administration of breast implant distillate or octamethylcyclotetrasiloxane (CS-D4)

Agent	3.5[a]	8.75	17.5	26.25	35
Distillate	0/5[b]	0/5	1/5	3/12	5/5
CS-D4	0/6	4/6	5/5	ND	6/6

ND, not determined.
[a]Dose in grams per kilogram administered intraperitoneally to female mice.
[b]Number dead per number injected by 14 days.

Histopathological studies. Complete autopsies were performed; organs were fixed in 10% buffered formalin, embedded, cut, and stained with hematoxylin and eosin for light microscopy. Lungs were inflated with the same fixative until they were fully expanded and fixed for at least 12 hr. To provide a semiquantitative assessment of tissue damage 4 days after treatment, we graded all sections of lung and liver and assigned a score to each section. Lesions were graded 0–4, with 0 representing no change and 4 representing severe changes. For lung, we evaluated interstitial inflammation, intraalveolar inflammation, edema, and focal hemmorhage. For liver, we evaluated extensive necrosis, individual cell necrosis, inflammation, microvesicular (hepatocyte) steatosis, mitosis, and apoptosis. Slides were read without knowledge of the treatment group (blindly).

Hydroxyl radical measurements by HPLC. Hydroxyl radical formation was measured by trapping the radical as 2,3-DHBA after administration of salicylic acid (100 mg/kg ip 1 hr before sacrifice) (*18*). Liver and lung tissues from soy oil-treated (control) and CS-D4-treated animals (8.75 g/kg) were collected at 1 day and 4 days for the quantitation of 2,3-DHBA. This hydroxyl adduct of salicylate is routinely used for quantification of hydroxyl radicals *in vivo* (*18*). Liver and lung tissues were homogenized in 0.25 M perchloric acid (PCA) containing 100 μM EDTA and 100 μM sodium metabisulfite. The acid soluble extracts (supernatants obtained by centrifugation at 10,000 rpm) were filtered through 0.2-μm filters, and the filtrate was analyzed for DHBA formation using HPLC/EC detection. DHBAs were separated on a reverse-phase column (DHBA-250, 250 × 3 mm, 5-μm particle size; ESA, Inc., Chelmsford, MA) using an isocratic mobile phase containing 50 mM sodium acetate, 50 mM citric acid, 8% methanol, and 2% isopropyl alcohol (adjusted to pH 2.5 with phosphoric acid). The flow rate was set at 0.5 ml/min and the oxidation of DHBAs was studied at 250 mV. Oxidation of salicylate was measured at 800 mV using a Coularray electrochemical detector (ESA). Results were normalized to the salicylate levels in the tissues and are expressed as the ratio of 2,3-DHBA to salicylate. For all of the above determinations, we performed two-tailed *t*-tests of values for treated mice versus those for soy oil controls.

Serum AST, ALT, and LDH levels were analyzed by a Vitros 950 chemical analyzer (Johnson & Johnson, St. Louis, MO).

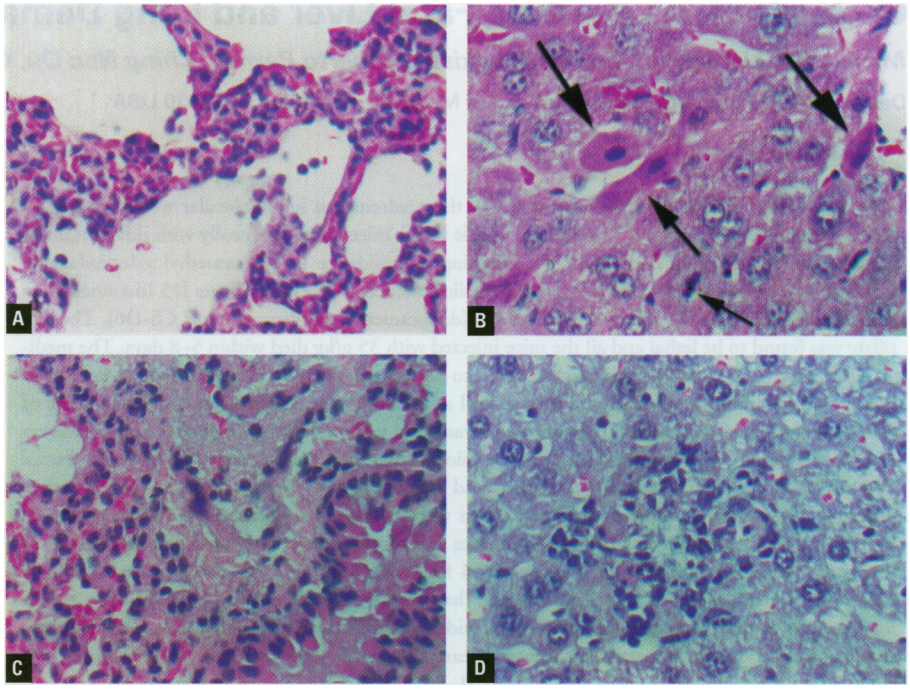

Figure 2. Histopathological changes in lung and liver of mice treated with breast implant distillate. (A) Section of lung from a mouse sacrificed 14 days after exposure to 0.5 ml (17.5 g/kg) breast implant distillate. There is thickening of the alveolar septae as a result of an inflammatory cell infiltrate, including lymphocytes and polymorphonuclear leukocytes. This and subsequent sections were stained with hematoxylin and eosin and photographed at 200×. (B) Section of liver from the same mouse shown in (A). Note individual cell necrosis (large arrows), mitotic figure (small arrow) and Kupffer cell hyperplasia. (C) Section of lung from a mouse sacrificed 4 days after exposure to 0.5 ml (17.5 g/kg) breast implant distillate. Note interstitial inflammation. A bronchiole containing eosinophilic proteinaceous material (edema) is present, and the parenchyma shows intraalveolar inflammatory cells. (D) Section of liver from the same mouse shown in (C). Individual cell necrosis, apoptotic bodies, and an acute inflammatory response are present.

Results

We exposed groups of female mice to different doses of distillate (3.5–35 g/kg) and found that all of the mice which received 35 g/kg distillate died in 5–8 days; 25% of the mice that received 26 g/kg distillate and 20% of the mice that received 17.5 g/kg distillate also died in this time period (Table 1). These experiments demonstrated that some or all of the components of the distillate are lethal with an LD_{50} for the distillate of ~28 g/kg (Table 1). Histopathology on tissues obtained from mice surviving to 14 days revealed lung, liver, and peritoneal changes. Lungs showed interstitial inflammation consisting of lymphocytes and neutrophils, edema, and thromboemboli in small to mid-size vessels. Some of these changes are shown in Figure 2A. In the liver, we observed individual hepatocyte necrosis, areas of regenerating hepatocytes, giant cells, clusters of proliferating oval or bile duct cells, Kupffer cell proliferation, and neutrophils

Table 2. Histopathological changes in liver and lung of mice treated with breast implant distillate

Dose (g/kg)	Liver						Lung			
	Extensive necrosis	Individual cell necrosis	Inflammation	Steatosis	Mitosis	Apoptosis	Interstitial inflammation	Intraalveolar inflammation	Edema	Focal hemorrhage
0	0/6	0/6	0/6	0/6	0/6	0/6	0/6	0/6	0/6	0/6
3.5	3/6 (+)	1/6 (+)	5/6 (+)	0/6	3/6 (+)	0/6	5/6 (+)	3/6 (+)	2/6 (+)	0/6
8.75	1/6 (+)	4/6 (+)	3/6 (++)	1/6 (+)	0/6	3/6 (+)	6/6 (++)	4/6 (+)	0/6	2/6 (+)
17.5	2/6 (++)	4/6 (+)	6/6 (+)	0/6	0/6	2/6 (+)	6/6 (++)	5/6 (+)	0/6	0/6
35	1/6 (+)	5/6(++)	4/6 (+)	2/6 (+)	1/6 (+)	2/6 (+)	5/6 (+++)	4/6 (++)	3/6 (+)	3/6 (++)

Values shown are numbers of mice with damage per number injected. The 0-dose group received 1 ml soy oil (~32 g/kg). Average grade of lesion: +, mild; ++, moderate; +++, moderately severe.

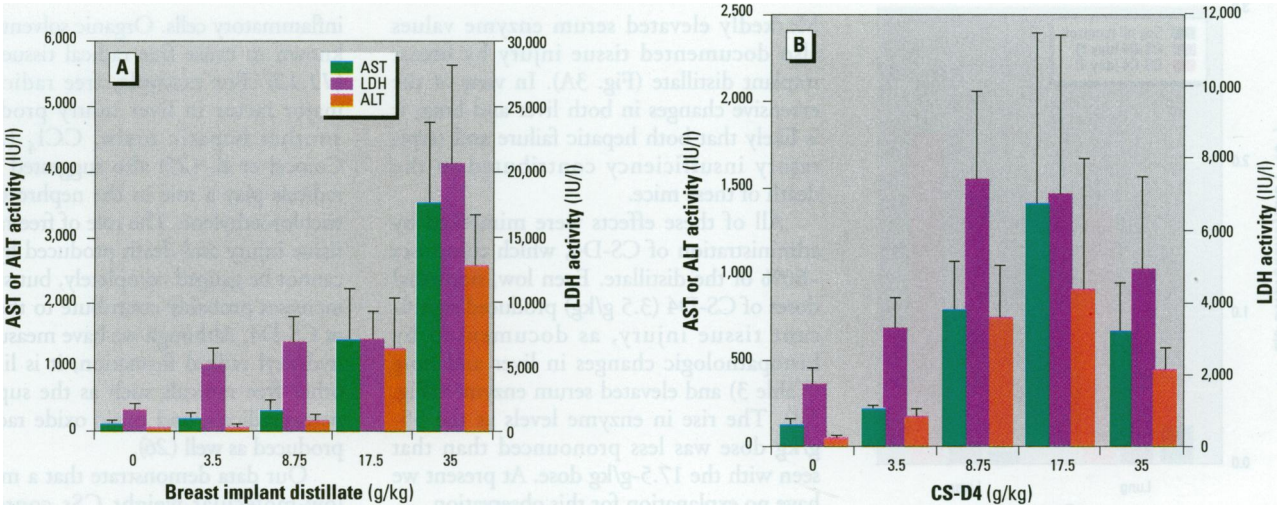

Figure 3. Serum alanine aminotransferase (ALT), aspartate aminotransferase (AST), and lactic acid dehydrogenase (LDH) enzyme activities after exposure to breast implant distillate and octamethylcyclotetrasiloxane (CS-D4). (A) Enzyme activities in serum obtained from mice 4 days after treatment with breast implant distillate (see "Materials and Methods"). For all enzyme determinations at all doses, values were significantly different from soy oil-treated mice ($p<0.04$). (B) Enzyme activities in serum obtained from mice 4 days after treatment with CS-D4. For all enzyme determinations at all doses, values were significantly different from soy oil-treated mice ($p<0.001$). Soy oil-treated mice values for enzymes obtained from two groups of controls (five control mice for distillate and five control mice for CS-D4; $n=10$) were averaged and are presented as control values. Values for soy oil-treated controls were as follows: ALT, 50.9 ± 5.95 IU/l; AST, 131.3 ± 27.5 IU/l; and LDH, 1,743 ± 457 IU/l. Four to six mice were used for the determination of enzyme activity for distillate or CS–D4-treated mice. Values are presented as the mean ± standard error.

predominantly around the central veins (Fig. 2B). Peritoneal surfaces were covered by acute and organizing inflammatory exudate (not shown). The severity of the changes increased with dose. No other pathologic changes were observed. Intraperitoneal injection of soy oil caused mild, focal, acute inflammation on the peritoneal surface of the liver and adjacent superficial parenchyma (not shown).

To examine more acute changes, we administered distillate (3.5–35 g/kg) to mice and sacrificed them at 4 days. In the lungs we found interstitial hypercellularity consisting primarily of neutrophils; intraalveolar macrophages, neutrophils, and lymphocytes; edema; and focal hemorrhage; occasionally we found vessels with thromboemboli (Fig. 2C). In the liver we found extensive inflammatory and necrotic changes. Figure 2D illustrates necrosis of individual liver cells and bile stasis. The histopathologic changes with dose are summarized in Table 2. Other markers of severe liver damage such as bilestasis and hepatocyte degeneration are seen only at high doses (data not shown). These data demonstrate that, in general, there is an increase both in the number of mice with individual changes and in the severity of these changes as the dose is increased. Taken together with the 14-day findings, the changes observed at 4 days in lung and liver represent a pattern of developing damage, regeneration, and repair. The peritoneal surfaces showed a dense acute inflammatory infiltrate that was also present on the serosal surface of abdominal organs. These changes increased in severity as a function of dose. No pathologic changes in other organs were observed. Serum ALT and AST rose sharply with dose; these enzymes are used clinically as markers of liver injury (Fig. 3A). LDH also rose with dose and is a nonspecific marker of tissue injury (Fig. 3A).

Because CS-D4 is the most abundant cyclosiloxane in breast implant distillate (see "Materials and Methods"), we administered CS-D4 alone to mice and found that it was lethal (Table 1). Mice died in 5–8 days with an LD_{50} of 6–7 g/kg (Table 1). Histopathology at 14 days on mice surviving CS-D4 treatment (3.5 and 8.75 g/kg) revealed changes similar to those seen with the distillate (not shown), but at the same dose, changes in CS–D4-treated mice tended to be more severe.

In a separate experiment, we evaluated acute tissue injury and serum enzyme levels after CS-D4 injection. Four days after injection we found severe pulmonary and hepatic lesions similar to those seen after injection of the distillate. These changes are summarized in Table 3, and reveal increasing damage as a function of dose. Injection of CS-D4 also resulted in large increases in serum enzymes (Fig. 3B). For example, in mice receiving 8.75 g/kg bw (slightly more than the LD_{50}) at 4 days, ALT, AST, and LDH values rose 15-, 6-, and 4-fold, respectively. It is also of interest that with CS-D4 mice, doses as low as 3.5 g/kg produced statistically significant ($p<0.001$) elevations in serum enzymes.

As a marker of free radical activity we measured hydoxyl radical formation in liver

Table 3. Histopathological changes in liver and lung of mice treated with octamethylcyclotetrasiloxane (CS-D4)

Dose (g/kg)	Liver						Lung			
	Extensive necrosis	Individual cell necrosis	Inflammation	Steatosis	Mitosis	Apoptosis	Interstitial inflammation	Intraalveolar inflammation	Edema	Focal hemorrhage
0	0/6	0/6	0/6	0/6	0/6	0/6	0/6	0/6	0/6	0/6
3.5	0/5	1/5 (++)	2/5 (+)	1/5 (+)	2/5 (++)	0/5	5/5 (++)	2/5 (++)	0/5	0/5
8.75	1/5 (+)	3/5 (++)	4/5 (+)	2/5 (++)	1/5 (+++)	3/5 (+)	5/5 (+++)	4/5 (+)	1/5 (+)	1/5 (+)
17.5	0/5	3/5 (+)	4/5 (+)	1/5 (+)	1/5 (++)	3/5 (++)	5/5 (++)	3/5 (++)	1/5 (++)	1/5 (++)
35	0/4	4/4 (++)	4/4 (++)	2/4 (+)	1/4 (+)	1/4 (+)	4/4 (+++)	4/4 (++)	2/4 (++)	2/4 (+)

Values shown are numbers of mice with damage per number injected. The 0-dose group received 1 ml soy oil (~32 g/kg). Average grade of lesion: +, mild; ++, moderate; +++, moderately severe.

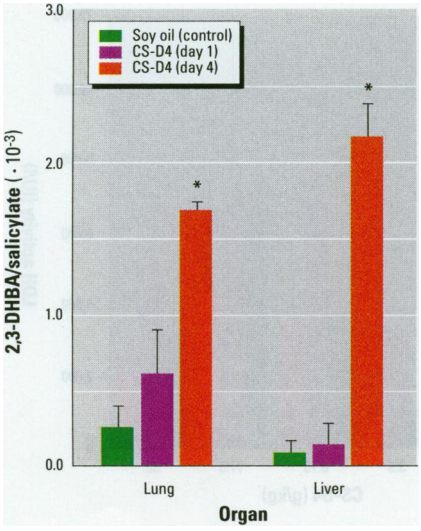

Figure 4. Hydroxyl radical formation in lung and liver of mice exposed to octamethylcyclotetrasiloxane (CS-D4). Values are expressed as the ratio of 2,3-dihydroxybenzoic acid (DHBA) to salicylate. Each value represents the mean ± standard error of data obtained from four individual mice. *p<0.001 as compared to control mice.

and lung of control (soy oil-injected) and CS–D4-injected (8.75 g/kg) mice by salicylate trapping (see "Materials and Methods"). On day 1, no increase in hydroxyl radical formation in either liver or lung was noted (Fig. 4). By day 4 there was a dramatic increase in radical formation with an ~20-fold increase in liver and an ~7-fold increase in lung (Fig. 4). These data indicate that large increases in hydoxyl radical formation occur well in advance of death.

Discussion

Our data provide evidence that CSs found in breast implants produce significant tissue injury and death when administered to female CD-1 mice. To the best of our knowledge, this is the first study demonstrating the *in vivo* toxicity of CSs. Injection of the distillate resulted in liver and lung damage and death in 5–8 days. Histopathologic evidence of damage was seen in mice that received low doses of distillate and survived 14 days and in mice that were sacrificed at 4 days (Fig. 2, Table 2). Markedly elevated serum enzyme values also documented tissue injury by breast implant distillate (Fig. 3A). In view of the extensive changes in both liver and lung, it is likely that both hepatic failure and respiratory insufficiency contributed to the death of these mice.

All of these effects were mimicked by administration of CS-D4, which comprises ~60% of the distillate. Even low, nonlethal doses of CS-D4 (3.5 g/kg) produced significant tissue injury, as documented by histopathologic changes in liver and lung (Table 3) and elevated serum enzymes (Fig. 3B). The rise in enzyme levels at the 35-g/kg dose was less pronounced than that seen with the 17.5-g/kg dose. At present we have no explanation for this observation.

We estimated the LD_{50} of CS-D4 to be ~6–7 g/kg. CS-D4 appears to be more toxic on a gram per kilogram basis than the distillate, even when the composition of the distillate (60% CS-D4) is taken into account. The reason for this apparent difference is unclear; however, most chemicals show a range of toxicity (see below), and the discrepancy is not large. Also, at present we do not know if other CSs in the distillate are toxic or may even be protective against the effects of CS-D4. This variability extends to the histopathology and enzyme findings and is probably accounted for by the variability seen in most animal experiments. The LD_{50} value of CS-D4 is in the same range for rodent LD_{50}s (oral) of well-studied toxic organic solvents such as CCl_4 (2.3–8.3 g/kg), trichloroethylene (2.4–5.7 g/kg), and hexachloroethane (4.5 g/kg) (*19–22*). Given some variation of LD_{50} values resulting from differences in species, strain, sex, and routes of administration, the value for CS-D4 indicates that this compound exhibits toxicity comparable to these other agents.

We also found dramatic increases in hydroxyl radical formation in the liver and lungs of CS–D4-treated mice (Fig. 4) by day 4, a time at which extensive inflammatory lesions were present. It is likely that these increases in free radicals result from the activity of both parenchymal and inflammatory cells. Organic solvents are also known to cause free radical tissue damage (*11,12*). For example, free radicals are a major factor in liver injury produced by another hepatic toxin, CCl_4 (*23, 24*). Cojocel et al. (*25*) also suggested that free radicals play a role in the nephrotoxicity of trichloroethylene. The role of free radicals in tissue injury and death produced by CS-D4 cannot be gauged completely, but such large increases probably contribute to the toxicity of CS-D4. Although we have measured only hydroxyl radical formation, it is likely that other free radicals such as the superoxide, peroxyradicals, and nitric oxide radicals are produced as well (*26*).

Our data demonstrate that a mixture of low-molecular-weight CSs contained in breast implants is highly toxic and that at least one specific compound, CS-D4, is toxic as well. The CSs have been considered inert, but there are data indicating that when silicone oils containing CSs are injected intraocularly, they produce local toxic effect (*11*). We have no evidence that these compounds are metabolized, but it is clear that they evoke strong biological responses. It remains to be determined if other CSs or the platinum found in implants produces tissue injury or death (*5*). Further, our studies have not evaluated possible long-term effects of CSs such as chronic inflammation, chronic pulmonary and liver disease, or neoplasia. Nevertheless, our results underscore the importance of a complete analysis of the toxicity of CSs.

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